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Short communication

Effect of backing films on the transdermal delivery of cyclobenzaprine patch

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ABSTRACT

The aim of this study was to investigate the effect of backing films on transdermal delivery of cyclobenzaprine patch. Different backing films were chosen to prepare the cyclobenzaprine transdermal patch. The cumulative amount of cyclobenzaprine released from different patches was evaluated *in vitro*. To investigate the interaction between cyclobenzaprine and backing films, the partitioning experiments and attenuated total reflectance Fourier transform infrared (ATR-FTIR) spectroscopy were performed. The cumulative amount of cyclobenzaprine released from the patch with Cotran™ 9700 as backing film was less than that of other patches with different backing films. Furthermore, the cumulative amount of cyclobenzaprine released from the patch with Cotran™ 9700 as backing film decreased significantly after 7 d storage at room condition. The partitioning experiments indicated a strong adsorption of cyclobenzaprine onto the Cotran™ 9700, which could explain the decrease of cumulative amount of cyclobenzaprine released from the patch with Cotran™ 9700 as backing film. According to the ATR-FTIR results, there was no interaction between Cotran™ 9700 and cyclobenzaprine. The effect of backing films on the release behavior of cyclobenzaprine transdermal patch was attributed to the adsorption of cyclobenzaprine onto the Cotran™ 9700.

1. Introduction

Cyclobenzaprine (CBZ), a centrally acting muscle relaxant, has an established efficacy and safety profile, with more than 30 years of practical application in the clinical low back pain setting [1,2]. Tablets and capsules were the only two dosage forms of CBZ available on the market [3]. The clinical application was limited by its compliance and side effect, such as sedation and somnolence. It is reported that the side effects were associated with high peak plasma concentration [4], which meant that maintaining a stable plasma concentration would result in a better control of side effect. It was known that transdermal delivery could be more possible to maintain a stable plasma

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concentration than tablets. Therefore, transdermal patch containing CBZ may decrease the side effect and improve the compliance greatly.

Backing film is an important component of the transdermal patch as it could provide an occlusive environment of skin. However, there are few reports about the effect of backing film on the formulation screening of transdermal patch. There was only one study that reported the interaction between the backing film and drug [5]. The aim of this study was to make sure if the backing film had an effect on the release of CBZ from a transdermal patch and if there was an interaction between the CBZ and backing film. In the study, different backing films consisted of different materials, chosen to evaluate the effects of the release of CBZ from the transdermal patch by release experiment *in vitro*, and the interaction between CBZ and backing film was investigated by partitioning experiment and ATR-FTIR.

2. Materials and methods

2.1. Materials

Cyclobenzaprine hydrochloride (CBZ HCl) was purchased from Far Top Pharmaceutical Co., Ltd. (Nanjing, China); DURO-TAK®87–4098 was purchased from Henkel (Holthausen, Germany); Release liner ScotchPak®9744, backing films Cotran™ 9700, Cotran™ 9718, Scotchpak™ 9733, Scotchpak™ 9723, Scotchpak™ HB-P-69731 were bought from 3M company (3M, USA). All other chemicals were of analytical grade.

2.2. The preparation of CBZ base

CBZ base was prepared in our laboratory as follows: CBZ HCl solution (50 mg/ml) was adjusted to pH 12 using NaOH solution (40 mg/ml), then, the CBZ base was extracted into ethyl acetate. The ethyl acetate was removed using a rotary evaporator. The purity of the obtained CBZ base was over 99.9% which was measured in the area normalization method by HPLC.

2.3. Preparation of patches

The drug-in-adhesive patches were prepared by the solvent evaporation technique [6]. CBZ and pressure-sensitive adhesive were dissolved in a minimum amount of ethyl acetate and mixed thoroughly with a magnetic bar for 2 h until it became homogeneous. The mixture was then cast onto a release liner. After that, the film was placed at room temperature for 15 min and then put into an oven set at 50 °C for 5 min. The solvent was removed and the dry film was coated with different backing films. The control patch in the release experiment was coated with the release layer as backing film.

2.4. In vitro release experiments

The two-chamber side-by-side glass diffusion cells (volume = 4.0 ml and effective diffusion area = 0.95 cm^2) were used in the release experiment. The test patch was pasted on the cellophane membrane and the cellophane membrane was mounted onto the diffusion cells. The cells were filled with 4 ml PBS and the solution was stirred at about 600 rpm and maintained at 32 ± 0.5 °C using a thermostatic water pump. At predetermined time interval, 2 ml samples were withdrawn and 2 ml fresh PBS was added. The samples were analyzed by HPLC method.

2.5. Partition of CBZ between backing film and medium

Backing films Cotran™ 9700, Cotran™ 9718, Scotchpak™ 9733, Scotchpak™ 9723, Scotchpak™ HB-P-69731 were weighed as 1 cm^2 pieces and placed in a 4 ml solution of CBZ (20 μg/ml) in a glass test tube, with 1:49 (v/v) of methanol and water as solvent. The test tubes were shaken for 24 h to reach equilibrium at 32 °C and the solution was analyzed by HPLC for drug content after equilibrium. Partition coefficients were calculated from CBZ concentration in the solution before and after equilibrium by the following equation: $K = (C_0 - C)/C$.

C_0 and C represent drug concentration in the CBZ solution before and after partitioning, respectively.

2.6. ATR-FTIR measurements

The backing film was cut into 1 × 1 cm square pieces and was divided into two groups. In one group, these backing films were treated as described in partition study. In the other group, the backing films were incubated in 4 ml of the blank solution (methanol: water, 1:49, v/v) for 24 h as control. Then, the backing films were dried at 40 °C for 2 h. The spectral measurements were performed with a Nicolet NEXUS 470 Fourier Transform Infrared Spectrometer (Thermo Nicolet, USA) equipped with an attenuated total reflectance (ATR) attachment.

2.7. Quantitative analysis

CBZ concentration was assayed using a Hitachi HPLC system (pump L-2130, UV-Vis detector L-2420, autosampler L-2200, T2000L workstation) equipped with a Diamonsil ODS (5 μm, 200*4.6 mm) at 290 nm as reported previously [7]. The mobile phase consisted of methanol/water/formic acid (300:200:1, v/v/v), and the flow rate was set at 1 ml/min.

2.8. Data analysis

Results of each experiment are presented as the mean ± SD of three or four experiments. Statistical analysis was conducted by using Student's t-test. A difference between data was considered significant when $P < 0.05$.

3. Results and discussion

3.1. In vitro release experiments

The process of drug traveling from patch to skin can be divided into two steps: drug release from the patch and then permeation through the skin [8]. As we have known, stratum corneum was the main barrier for transdermal drug delivery and it was not in touch with the backing film directly. So the effect of

Table 1 – Partition coefficients of CBZ from the backing films to the vehicle (n = 3, mean ± SD).

Backing film	9700	9718	9733	9723	69731
Partition coefficient	0.97 ± 0.25	0.14 ± 0.07	0.27 ± 0.08	0.32 ± 0.08	0.26 ± 0.06

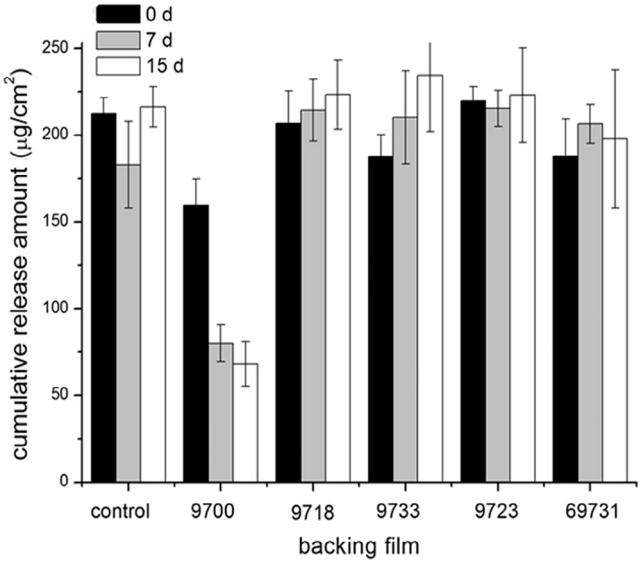

Fig. 1 – The release profiles of CBZ patches with different backing layers and the patches were stored for 0 day, 7 days and 15 days after preparation, respectively. Data were presented as the mean ± SD (n = 3 or 4).

backing film on transdermal drug delivery was mainly dependent on the release process. *In vitro* release experiment would be more suitable compared to permeation experiment in investigating the effect of backing films on transdermal patch. The CBZ transdermal patches with different backing films were prepared and each patch was divided into 3 groups. The release experiment was performed immediately for the patches in group 1. For the patches in groups 2 and 3, these were stored for 7 d and 15 d before the release experiment, respectively. As shown in Fig. 1, the cumulative release amount of patch prepared with Cotran™ 9700 was less than that of the control patch and the difference between them was statistically significant ($P < 0.05$). The cumulative release amount of control patch was similar to that of the patches with other backing films. Furthermore, the release amount of the patch prepared with Cotran™ 9700 further decreased after 7 d storage at room condition. There was no significant difference in the cumulative release amount of other patches after storage. The only difference between the control patch and the patch prepared with Cotran™ 9700 was the backing film. This indicated that the backing film may be responsible for the difference in cumulative release amount of the two patches. And in other words, Cotran™ 9700 had some effects on CBZ release from transdermal patch.

3.2. *Partition of CBZ between backing film and medium*

The results of the release experiment suggested that there may be some interaction between CBZ and backing films. To compare the affinity between the CBZ and different backing films, the partitioning experiments were performed. Partitioning experiment was a time-saving, simple and convenient method to confirm the affinity between CBZ and backing film, which was often used in the determination of drug solubility in the PSA matrix [8,9]. The partition coefficient of CBZ between the same medium and different backing film was used to compare the affinity between CBZ and different backing films. The higher partition coefficient suggested the stronger affinity between CBZ and backing film. As shown in Table 1, it was inferred that the affinity between CBZ and Cotran™ 9700 was significantly stronger than other groups. And the results agreed with the results of release experiment. The affinity between CBZ and Cotran™ 9700 might be the reason for the less cumulative release amount of the patch prepared with Cotran™ 9700. It can be inferred that it took time to reach equilibrium of adsorption. And this may be the reason for the decreased release profiles of the patch after storage.

3.3. *ATR-FTIR measurements*

The results of the release experiments and partitioning experiments both indicated the potential interaction between CBZ and Cotran™ 9700. The results were in accordance with the results of experiments done by Liu Nannan [5]. In her study, it was concluded that intermolecular hydrogen bonds formed between Cotran™ 9700 and the drug. As known, ATR-FTIR was a classical spectroscopic method for studying the hydrogen bonding between complexes [10,11]. To elucidate the interaction between CBZ and Cotran™ 9700, ATR-FTIR was used in the following study. As can be seen from Fig. 2, there was no difference in IR spectrum of the control (Fig. 2A) and the backing

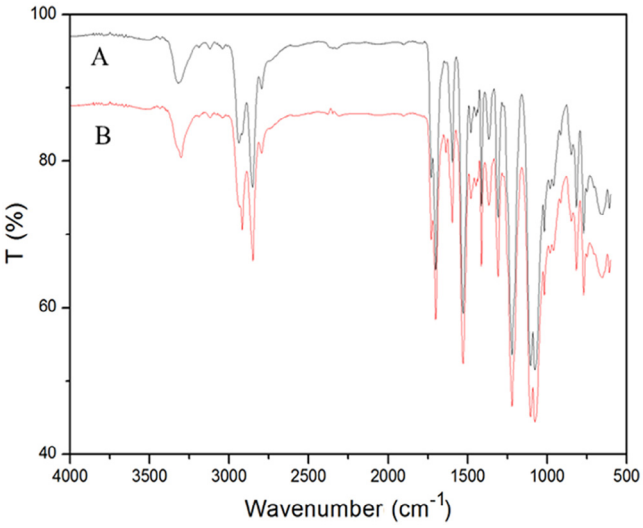

Fig. 2 – ATR-FTIR spectra of the backing film Cotran™ 9700 control (A) and after treated by CBZ solution (B).

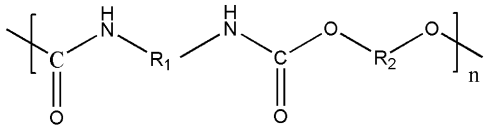

Fig. 3 – The main-chain structure of polyurethane.

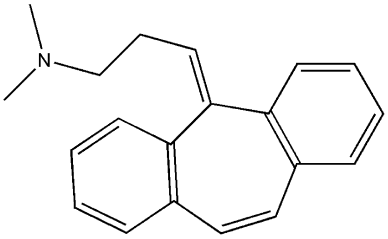

Fig. 4 – The chemical structure of cyclobenzaprine.

film Cotran™ 9700 was incubated in CBZ solution (Fig. 2B). It was suggested that there was no hydrogen bonding between CBZ and Cotran™ 9700. In Liu's study, the drug has 4 H bond acceptors and the polyurethane (shown in Fig. 3) in the structure of Cotran™ 9700 serves as H bond donor. However, CBZ (shown in Fig. 4) has only 1 H bond acceptor. It can be inferred that intermolecular hydrogen bonding was more difficult to form between CBZ and Cotran™ 9700. Backing film Cotran™ 9700 is a soft, conformable, melt-blown polyurethane, and is nonwoven that has multi-directional stretch properties. It is indicated that the backing film Cotran™ 9700 is porous and the adsorption may exist in the porous structure. The adsorption of CBZ onto Cotran™ 9700 may be responsible for the less cumulative release amount of transdermal patch.

4. Conclusion

The study investigated the effect of backing films on the release of transdermal patch containing CBZ by *in vitro* release experiments, partitioning experiments and ATR-FTIR methods. It can be concluded that the adsorption of CBZ onto the Cotran™ 9700 was responsible for the decreased release profiles of the CBZ transdermal patch. The cumulative release amount further decreased after 7 days of storage and might be because it took time to reach equilibrium of adsorption. The adsorption between drug and backing film might have great effect on the transdermal delivery and backing film should be taken as an important factor in the formulation screening.

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